UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/992,914	12/18/1997	EIJIRO WATANABE	0020-4348P	4405

2292 7590 06/27/2008

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	

NOTIFICATION DATE	DELIVERY MODE
06/27/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	08/992,914	WATANABE ET AL.	
	Examiner	Art Unit	
	David H. Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,43 and 46-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6 and 43* is/are allowed.

6)☒ Claim(s) *46-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Attachment sequence alignment*.

DETAILED ACTION

1. The finality of the Office action mailed 1 December 2005 is withdrawn in view of the Remand from the Board of Patent Appeals mailed 30 May 2008. The Board had interpreted Applicants' arguments concerning introduced evidence as a request to reopen prosecution.

2. The arguments addressed herein are those filed in the Appeal Brief on 26 December 2006. The response to said arguments are those put forth by the Examiner in the Examiner's Answer mailed on 16 May 2007.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

4. Claims 46-51 remain rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility. The arguments addressed herein are those filed in the Appeal Brief on 26 December 2006.

Applicant argues that the present specification expressly describes that the present invention is related to isolated nucleic acids encoding raffinose synthase enzymes (see, page 2, lines 18-20). The specification describes raffinose synthase enzymes as catalyzing the rate-limiting step in raffinose oligosaccharides, which oligosaccharides are important in the food value of plants. The specification explains that raffinose synthases are present in plants of widely divergent species and urges that manipulation of the raffinose content of a plant, by manipulation of the amount of

raffinose synthase expressed in the plant, is useful for making plants more healthy as foods, referring to pages 1-2 of the specification. Applicant argues that the specification also alleges that this manipulation can be in the form of over-expression of a raffinose synthase enzyme, or by decreasing the expression of raffinose synthase using antisense technology or the like, referring to page 26, lines 4-17 (of the specification). Applicant further argues that the Examiner does not at all challenge this asserted utility of the invention, thus it must be accepted that the asserted utility of the invention is credible, substantial and specific, and that such is consistent with the present allowance of claims 3 and 46. Page 6, 1st and 2nd paragraphs of the Appeal Brief.

These arguments are not found to be persuasive. The instant rejection is directed to the utility of the specific species of claims 46-51. The utility of the allowed claims directed to the species of SEQ ID NO: 1 encoding SEQ ID NO: 2, a broad bean raffinose synthase, has been established. The amino acid sequences of SEQ ID NO: 6 and 8 are incomplete and do not teach a full-length protein, and hence are not functional. SEQ ID NO: 6 is 586 amino acids in length and SEQ ID NO: 8 is only 271 amino acids in length. One skilled in the instant art would immediately recognize that SEQ ID NO: 6 or 8 are too short to teach a complete, functional enzyme and would immediately recognize that both amino acid sequences are missing the N-terminal regions that would start with a methionine. The amino acid sequence of SEQ ID NO: 4, encoded by SEQ ID NO: 3, is asserted to be a soybean raffinose synthase enzyme. However, Applicant has provided no evidence of such a function, and Osumi *et al* (U.S. Patent 6,891,084) teach a soybean raffinose synthase enzyme at SEQ ID NO: 24, (a

sequence alignment attached hereto) shows only 32.9% sequence identity at the amino acid level to Applicant's SEQ ID NO: 4. Applicant's own arguments of record concerning structure-function relationship among raffinose synthase enzymes that distinguish them from stachyose synthase enzymes suggests that Applicant's SEQ ID NO: 4 does not teach a raffinose synthase. The Nagasawa Declaration, filed under 37 CFR § 1.132 on 12 September 2005, states that the homologies between RFSs (Raffinose Synthases) and SIP (Seed Imbibition Protein) are less than 40%. The Nagasawa Declaration states that the homologies between RFSs and STSs (Stachyose Synthases) are not higher than 45%. The Nagasawa Declaration states that on the other hand, the homologies among RFSs are all 50% or higher. The Nagasawa Declaration states that thus, the homologies among RFSs are higher than those homologies between RFSs and SIP and between RFSs and STSs (see page 7 of the Nagasawa Declaration). As a result, it is apparent that the amino acid sequence of SEQ ID NO: 4 fails to teach a functional raffinose synthase enzyme due to its low sequence identity of less than 50% to an established soybean raffinose synthase enzyme. It is equally apparent that both SEQ ID NOs 6 and 8 are too short and thus do not describe functional raffinose synthase enzymes.

Applicant argues that the Examiner's position is incorrect and that the present record contains sufficient evidence that one of ordinary skill in the art is able to distinguish a RFS from a STS by analysis of the overall degree of amino acid sequence similarity of any desired protein to the amino acid sequence of one of the SEQ ID NOs: 2, 4, 6 or 8 of the present application. Applicant further argues that the present claims

46-51 recite defined amino acid sequences of specific nucleotide sequences that are one sequence that may encode the defined amino acid sequence. The nucleic acid sequences are those of the raffinose synthase cDNAs cloned from soybean, Japanese artichoke and corn, as in Examples 7, 9 and 11 of the specification; the amino acid sequences are those obtained by translation of the cDNA sequences. Paragraph spanning pages 6-7, and page 7, 2nd paragraph of the Appeal Brief.

These arguments are not found to be persuasive, and have been addressed above. Specifically, the percent identity of the cited sequences does not meet the standard set forth in Applicants won declaration (the Nagasawa Declaration).

Applicant argues that as to the "structure-function relationship" defining the genus of the nucleic acids encoding a raffinose synthase, Applicant does not see how this applies to the present claims 46-51 (because the claims are limited to particular defined sequences). Applicant further argues that a distinct structure of a particular amino acid sequence or of a particular nucleic acid sequence is recited in these claims. Applicant further argues that the present specification, and the record of the present application, makes clear that the question of utility before the Board relates to whether the amino acid sequence of a particular protein is sufficient for determining whether or not the protein would be more likely than not to possess raffinose synthase activity. Applicant also argues there is substantial evidence of record that one of ordinary skill in the art can distinguish a RFS enzyme from a STS enzyme solely on the basis of amino acid sequence. Applicant argues that Applicant has previously provided phylogenetic analyses of the amino acid sequence of RFSs and STSs and has established that the

degree of sequence homology among RFSs and among STSs is significantly higher than the degree of homology between RFSs and STSs. This relationship is robust to analysis using two different sequence identity determination algorithms. See, Table 3 attached to the Amendment filed November 15, 2004 and Table 2 attached to the Amendment filed February 25, 2004, both presented in Evidence Appendix B. To this evidence, Applicant has added the Declaration of Mr. Akitsu Nagasawa also provided in Evidence Appendix B. Mr. Nagasawa attests to the methodology used to generate the data in Tables 2 and 3 and presents an additional analysis using yet a third approach to calculating sequence identity. See page 7, 3rd and 4th paragraphs of the Appeal Brief.

Applicant additionally argues that the argument of the Examiner is not persuasive, not the least because it ignores that the present specification includes a second amino acid sequence, SEQ ID NO: 2, demonstrated to exhibit raffinose synthase activity and three additional sequences that are compared to that sequence. Applicant's argument is that the sequences independently described by the specification are identifiable as a group separate from sequences that form another group of sequences, which happen to be stachyose synthases (or from a second group of SIPs, see the Declaration of Mr. Nagasawa). See page 8, 4th paragraph of the Appeal Brief.

These arguments are not found to be persuasive. The issue concerning amino acid sequences of SEQ ID NO: 6 and 8, i.e. that the sequences are incomplete is outlined above. See *Brenner v. Manson*, 383 U.S. 519 (1966), which states "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent

monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point--where specific benefit exists in currently available form--there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." As for SEQ ID NO: 4 (instant claims 46 and 47) Applicant's assertion is based on facts that were not known until after the filing of the instant Application. In Table 1 of The Nagasawa Declaration, six (6) proteins are listed as raffinose synthases, Sc-02 and Sc-04 being taught in the instant application, and Aj-05 being the cucumber raffinose synthase of the prior art acknowledged in the Information Disclosure Statement filed on 5 March 2001. The proteins Sc-03 and Sc-05 are taught in a related application assigned to the Applicant, which has a foreign priority of 30 April 1998, and the PsRFS (pea Raffinose Synthase) was taught by Peterbauer *et al* in 2002. Given the U.S. filing date of 18 December 1997 of the instant application, only two complete and confirmed raffinose synthase enzyme amino acid sequences, and one being the asserted raffinose synthase of SEQ ID NO: 4, were known in the art at the time of the instant invention. The Examiner has established the fact that at the time of the instant invention, only one other plant raffinose synthase "gene" was know in the art, that being from cucumber and disclosed in US Patent 6,166,292 (see Office action mailed 6 February 2002, page 5). It is unclear how Applicant at the time of filing could make an assumption of function of an encoded "enzyme" using sequence similarity without actually showing the expressed encoding nucleic acid actually produced a raffinose synthase at the time of the instant invention (page 3 of the Office action mailed on 1 December 2005). The Examiner's argument is

based on the fact that it appears that only one of Applicant's amino acid sequences is actually a raffinose synthase (SEQ ID NO: 2), and thus Applicant's assertion of a structural-functional relationship is based on the comparison of only two amino acid sequences.

Claim Rejections - 35 USC § 112

5. Claims 52-74, 77 and 82-86 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The arguments addressed herein are those filed in the Appeal Brief on 26 December 2006.

As stated above, the rejection of claims 46-51, 75 and 76 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description has been withdrawn. As this rejection is no longer directed to claims 46-51, Applicant's arguments are moot, as they relate to these claims. The instant rejection, as directed to claims 52-74, 77 and 82-86 is maintained.

Applicants argue that the claims are directed to nucleic acids "comprising" the sequences 5 and 7, encoding the partial RFS proteins of SEQ ID NOs: 6 and 8. Nonetheless, these sequences must be taken as described to this extent. Applicant states that the working Examples 5-11 of the specification provide description of the experiments in which the cDNAs encoding raffinose synthases from broad bean, soybean, Japanese artichoke and corn are obtained. Applicant further argues that the experiments of Examples 5-9 are described in a manner that indicates that the full-length cDNA is cloned, and thus the coding portion from amino terminal to carboxy-terminal of the raffinose synthase protein is obtained. See, e.g. Example 6 at page 32,

in which use of data from the 5' end of a first cDNA clone are used to construct a primer for extending the cDNA at least to the end of the coding portion of the corresponding mRNA. Applicant additionally argues that the amino acid sequence set forth in SEQ ID NO: 4 is complete, and SEQ ID NOs: 6 and 8 are partial protein sequences, but sufficiently long to allow determination that they encode a RFS, or at least part of one, by their degree of overall identity to the known RFS of SEQ ID NO: 2. See page 11, 1st and 2nd paragraph of the Appeal Brief.

These arguments are not found to be persuasive. As pointed out above, Osumi *et al* (U.S. Patent 6,891,084) teach a soybean raffinose synthase enzyme at SEQ ID NO: 24, (a sequence alignment attached hereto) that shows only 32.9% sequence identity at the amino acid level with Applicant's SEQ ID NO: 4. Applicant's own arguments of record concerning structure-function relationship among raffinose synthase enzymes that distinguish them from stachyose synthase enzymes would suggest that Applicant's SEQ ID NO: 4 does not teach a raffinose synthase due to its low sequence identity. See the Nagasawa Declaration filed under 37 CFR § 1.132 on 12 September 2005, page 7. As directed to the partial sequences of SEQ ID NOs: 6 and 8, these sequences fail to adequately describe an isolated nucleic acid encoding a raffinose synthase enzyme. The amino acid sequences of SEQ ID NO: 6 and 8 are incomplete and do not describe a full-length protein, and hence are not functional. SEQ ID NO: 6 is 586 amino acids in length and SEQ ID NO: 8 is only 271 amino acids in length. One skilled in the instant art would immediately recognize that SEQ ID NO: 6 or 8 are too short to describe a complete, functional enzyme and would immediately

recognize that both amino acid sequences are at least missing the N-terminal regions that would start with a methionine. See *In re Wallach*, 71 USPQ2d 1939 (CA FC 2004), at 1940: Claims in application directed to isolated DNA molecules encoding proteins that inhibit cytotoxic effects of tumor necrosis factor were properly rejected for failure to satisfy written description requirement of 35 U.S.C. § 112, since applicants claimed nucleic acids encoding protein for which they provided only partial sequence, and without approximately 95 percent of amino acid sequence that applicants did not disclose, it cannot be held that DNA molecules claimed in application have been described, since applicants' contention that they were in physical possession of protein does not establish their knowledge of that protein's amino acid sequence or any of its other descriptive properties, even though amino acid sequence is inherent property of protein, and since application does not provide adequate functional description, in that, with only partial amino acid sequence disclosed, chemical structure of nucleic acid molecules that can serve function of encoding protein's amino acid sequence cannot be determined. Applicant has not established the function of the amino acid sequences of SEQ ID NO: 6 or 8. The Examiner notes that claims 53-58, 61, 62, 64, 66, 70-72, 74 and 77 are directed to isolated nucleic acids and compositions comprising isolated nucleic acids from laminaceous and monocotyledonous plants encoding raffinose synthase only described by a possible method of making, wherein Applicants have not adequately described a single species of the genus claimed.

Applicant argues that Applicant's burden is to establish, by a preponderance of the evidence, that the amino acid sequences of SEQ ID NOs: 4, 6 and 8 represent

proteins having raffinose synthase activity. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Applicant further argues that the particular amino acid sequences in question were obtained by a cloning method generally accepted in the art as useful for cloning functionally homologous proteins across species lines. Comparison of the full-lengths of these sequences against SEQ ID NO: 2, known to encode a raffinose synthase, shows that they have a degree of sequence identity accepted by one of ordinary skill in the art to establish that they are likely to be raffinose synthase enzymes, as opposed to stachyose synthases or seed imbibition proteins. This conclusion is supported by the Declaration testimony of Mr. Nagasawa and furthermore, Mr. Nagasawa's method of analysis has been shown to be robust to the application of three different computational methods. Against this evidence, the Examiner has raised only his opinion supported by an analysis that is incomplete. Page 12, 2nd paragraph of the Appeal Brief.

Applicant argues that it is entirely proper to claim an invention in product-by-process terms, *Fiers v, Revel*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Applicant further argues that claims 53-58 in effect describe the working examples of the specification, which represent an actual reduction to practice of four different species of the invention. Applicant additionally argues that therefore, it must be accepted that the process described in claims 53-58 is effective for obtaining operable embodiments of the invention. Page 13, 3rd paragraph of the Appeal Brief.

This argument is not found to be persuasive. Applicant has not provided a preponderance of evidence indicating that the amino acid sequences have raffinose synthase activity. The Examiner has established that at the time of the instant invention,

one skilled in the art would have required evidence of specific function for a putative raffinose synthase because of the similarity to both stachyose synthases and seed imbibition proteins. The issue of whether it is proper to claim an invention in product-by-process terms is irrelevant to the instant rejection. The issue is whether Applicant was in possession of the invention as broadly claimed. The process of making must adequately describe the product made in order to adequately describe the product. See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism. At 1406, the court states that a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Applicant has not recited structural features common to the genus of raffinose synthases. Their sole evidence lies with the purported assertion of sequence similarity, which is flawed as discussed above.

Applicant argues that contrary to the Examiner's assertion that the claims (specifically, claims 53-58) do not include any correlation between structure and function, the claims include two structural features that are connected to operable embodiments. First, there are the primer sequences utilized in the process. Applicant

argues that these primers represent portions of the raffinose synthase cDNAs of the family of plants recited that are conserved among the raffinose synthases from that family, as evidenced by their successful use in isolating cDNAs encoding raffinose synthases from plants of those families. Applicant further argues that the primer sequences are incorporated into the product nucleic acid, and so represent at least a minimal specific sequence in the product. Applicant also argues that the claims recite that the nucleic acid obtained as the amplification product must hybridize to a nucleic acid that is known to encode a raffinose synthase under conditions accepted in the art to constrain the hybridizing sequence to those having a high degree of sequence identity. Paragraph spanning pages 13-14 of the Appeal Brief.

Applicant argues that because claims 53-58 include structural features correlated with function of the obtained nucleic acid as a raffinose synthase, and because the working examples of the specification demonstrate actual reduction to practice of the invention as set forth in claims 53-58, Applicant submits that these claims are well-supported by the specification. Accordingly, the rejection of claims 53-58 under 35 U.S.C. § 112, first paragraph, for alleged tack of written description support in the specification, should be reversed. See page 14, 3rd paragraph of the Appeal Brief.

These arguments are not found to be persuasive. No specific sequences are claimed and Applicant has failed to describe the genus of leguminous, laminaceous or a monocotyledonous plant raffinose synthase encoding nucleic acids as broadly claimed. There are about 65,000 monocot species known world wide, and the Leguminosae has between 16,000 to 19,000 species. One skilled in the art would not have recognized

that Applicant was in possession of such a genus of nucleic acids isolated from a plant as broadly claimed. As stated above, *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism. Leguminous, laminaceous and monocotyledonous plants encompass a vast number of species to which the instant claims are directed.

Applicant argues that the Examiner has not set forth any particular explanation of any separate grounds of rejection other than those explained above, and therefore the various arguments applied to claims 52 or 53, as may be applicable, should be applied to these claims as well, and that the Board should consider that the plasmid aspect of claims 65 and 66 is thus deemed well described by the specification and the instant rejection should be reversed as to claims 65 and 66. Page 15, 2nd paragraph of the Appeal Brief. Applicant argues that the Board should consider that the promoter aspect of claims 59-62 is thus deemed well-described by the specification and the instant rejection should be reversed as to claims 59-62. See the paragraph spanning pages 14-15 of the Appeal Brief. Applicant further argues and that the Board should consider that the transformant and host organism aspects of claims 63, 64 and 67-72 are thus deemed well described by the specification and the instant rejection should be reversed as to claims 63, 64 and 67-72. See page 15, 3rd paragraph of the Appeal Brief.

Applicant additionally argues that the Board should consider that the metabolic transformation aspect of claim 73 is thus deemed well described by the specification and the instant rejection should be reversed as to claim 73. See the paragraph spanning pages 15-16 of the Appeal Brief. Additionally, Applicant states that the Board should consider that the metabolic transformation aspect of claim 74 is thus deemed well-described by the specification and the instant rejection should be reversed as to claim 74. See page 16, 2nd paragraph of the Appeal Brief.

Applicant argues that claim 77 represents a subgenus compared to claim 53, in that the plant from which the template nucleic acid obtained is more specifically defined to the level of a species. Applicant further argues that compared to claim 53, claim 77 more closely describes the working examples 5-11, and so to that degree must be acknowledged to be well-described by the specification. See page 16, 4th paragraph of the Appeal Brief.

Applicant argues that the relatively high degree of identity between SEQ ID NOs: 2 and 4 very clearly establishes that SEQ ID NO: 3 encodes a RFS protein, rather than a STS or SIP. Applicant further argues that these are the sequences that are "full-length" and demonstrated to or thus very likely to represent an active enzyme (or encode one), accordingly the subject matter of claims 84 and 85 must be deemed well described by the present specification. See page 18, 1st paragraph of the Appeal Brief. Applicant argues that the relatively high degree of identity between SEQ ID NOs: 2 and 4 very clearly establishes that SEQ ID NO: 3 encodes a RFS protein, rather than a STS or SIP. Applicant argues that furthermore, these are the sequences that are "full-length"

and are either demonstrated to are very likely to represent an active enzyme (or encode one). Accordingly the subject matter of claim 86 must be deemed well described by the present specification. See page 18, 2nd paragraph of the Appeal Brief.

These arguments are not found to be persuasive. Because the claimed chimeric gene comprises the isolated nucleic acid of claims 52-58, hence claims 59-62 lack adequate written description for the same reasons. In the same manner, the plasmid of claims 65 and 66, the transformant and host organism of claims 63, 64 and 67-72, and the metabolic transformation aspect of claim 73 or 74 lack adequate written description because they comprise nucleic acids that have not been adequately described. The Examiner has not argued that the promoter aspect lacks adequate written description, just the nucleotide sequence coding for an amino acid sequence of a raffinose synthase as broadly claimed lacks adequate written description.

6. Claims 46-77 and 78-86 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding the amino acid sequence of SEQ ID NO: 2, a chimeric nucleic acid comprising said isolated nucleic acid, a transformant comprising said chimeric nucleic acid, a plasmid comprising said nucleic acid, a host organism either a microorganism or plant comprising said plasmid, and a method of metabolic modification of a plant comprising introducing said isolated nucleic acid, does not reasonably provide enablement for an isolated nucleic acid encoding the amino acid sequence of SEQ ID NO: 4, 6 or 8, or an isolated nucleic acid that hybridizes with a complement to said isolated nucleic acid isolated from any

leguminous, laminaceous or monocotyledonous plant. The arguments addressed herein are those filed in the Appeal Brief on 26 December 2006.

Applicant argues that the Examiner has only addressed the predictability in the art, in the sense that his position is that, because the specification only actually demonstrates biological activity as a raffinose synthase for SEQ ID NO: 2, and the degree of sequence identity among the amino acid sequences identified in the working examples is as low as 60%, [and that] Applicant cannot reliably assign the biochemical activity of a raffinose synthase to the amino acid sequences of SEQ ID NOs: 4, 6 and 8. To the degree that the Examiner has addressed the other factors to be considered at all, it is only to describe his disagreement with positions on these issues expressed by Applicant. See page 20, 1st paragraph of the Appeal Brief.

Applicant argues that the skilled artisan can follow detailed teachings in the specification of how to clone, express and evaluate DNAs that are likely to encode functional raffinose synthase enzymes. Applicant argues that it is true that it is unpredictable whether any individual clone made in an experiment will include a DNA encoding a functional enzyme, but it is not unpredictable whether the skilled artisan would succeed in identifying at least one functional DNA in an experiment as a whole, to the contrary, it is very likely that the skilled artisan would find a cloned DNA encoding a functional enzyme by following the teachings of the specification. See page 23, 4th paragraph of the Appeal Brief.

These arguments are not found to be persuasive. As directed to claims 46-51, since the claimed invention is not supported by either a substantial asserted utility or a

well established utility for the reasons set forth on the record, one skilled in the art clearly would not know how to use the claimed invention. The Examiner has addressed, by the nature of the rejection, the breadth of the claims, the nature of the invention, and the state of the prior art, and additionally addressed the predictability of the art at the time of the invention. All of these factors were considered as they relate to isolation of nucleic acids encoding plant raffinose synthase enzymes. The Examiner has provided evidence that one of skill in the instant art would require more than sequence similarity as evidence of function, contrary to Applicant's assertion. See Duggleby 1997 and Richmond *et al* 2000, Plant Physiology 124: 495-498, at the paragraph spanning left and right column on page 497 (previously cited). The number of species of isolated nucleic acids within the scope of the claims would have required undue trial and error experimentation to make and use. There are about 65,000 monocot species known world wide, and the Leguminosae has between 16,000 to 19,000 species. Given the vast breadth of instant claim 52, for example, it would have required undue trial and error experimentation to make and use the invention as broadly claimed.

Applicant argues that the Examiner's analysis of the question of undue experimentation looks only at the factor of whether working examples of the claimed invention are described in the specification and an assertion that it is unpredictable that a particular nucleic acid produced according to the teachings of the invention would in fact exhibit raffinose synthase activity. Applicant further argues that this analysis is legally insufficient to establish a *prima facie* lack of enablement, as the Examiner fails to consider the breadth of the claims, the nature of the invention, the level of ordinary skill

in the art, the quantity of the experimentation needed, the guidance provided by the specification (other than the presence or absence of working examples) and the state of the art at the time the invention was made. Furthermore, Applicant argues that the kind of predictability, a prior knowledge of functionality of the enzyme obtained using the methods of the invention, is not the kind of predictability envisioned by the Court in *Wands*. See page 21, 2nd paragraph of the Appeal Brief.

Applicant argues that the art of molecular biology, in particular the art of expression of recombinant proteins, is one in which the artisan of ordinary skill expects to perform a few weeks or months of experimentation in generating variants of a protein, then isolating clones encoding those variants and then (perhaps) re-cloning the isolated variants into vectors for expressing a protein, and then screening expressed proteins for activity. See page 21, 4th paragraph of the Appeal Brief.

Applicant argues that the artisan of ordinary skill in the art of cloning and expressing recombinant proteins is generally accepted as one having a PhD. degree and perhaps higher. Such a person is skilled in the design and performing of experiments for isolating DNA clones and for screening them for a desired property, for example encoding a protein having a particular activity. See page 21, 5th paragraph of the Appeal Brief.

Applicant argues that the amount of experimentation needed to practice the present invention is not unduly large or burdensome. Applicant additionally argues that the practitioner must isolate a template genomic DNA from an organism, perform a polymerase chain reaction using primers described in the specification to generate an

amplified fragment, clone that fragment into an expression vector, express the encoded protein and then screen the protein for activity as a raffinose synthase. All of these steps are either well-known in the art or described in detail in the specification and furthermore are expected to be performed by the artisan of ordinary skill. Applicant argues that at the time the invention was made, the state of the art of molecular biology was such that the various laboratory operations that must be performed to carry out the experimentation required to practice the instant invention, i.e. cloning of DNA molecules and expressing them in a host cell, were routine. Also, polymerase chain reaction amplification of nucleic acids was routine. The raffinose content of a number of organisms, especially including plants and some algae, was known. The biochemistry of raffinose synthesis in plants had been established, and the role of raffinose synthases as rate-limiting of raffinose production was known. See page 22, 1st to 3rd paragraphs of the Appeal Brief.

These arguments are not found to be persuasive. The *Wands* factors put forth by the Court takes into consideration the general skill of one in the art at the time of the invention. The Examiner has provided evidence that one of skill in the instant art would require more than sequence similarity as evidence of function, contrary to Applicant's assertion. The art teaches that raffinose synthase enzymes have high overall amino acid sequence homology with seed imbibition proteins and stachyose synthases, hence amino acid sequence similarity cannot be used to assert function (see Peterbauer *et al* 2002, Planta 215: 839-846, see page 840, left column and page 841, right column; previously cited). Given the breadth of the claimed invention, for example claim 53

directed to nucleic acids encoding a raffinose synthase enzyme isolated from any leguminous, laminaceous, or monocotyledonous plant using specific primers, and the number of species that fall within these groups of plants, it would have required undue trial and error experimentation at the time of the instant invention to screen and confirm the function of such a broad genus of isolated nucleic acids as claimed. Additionally, it is unclear from the instant specification that the recited primers would actually identify a raffinose synthase encoding nucleic acid from a plant species other than that of the homologous plant, if in fact the taught nucleic acid from which the primers were produced actually encodes a raffinose synthase enzyme which has been brought into question above. The instant application provided no guidance on how to distinguish isolated nucleic acids encoding raffinose synthase from those encoding stachyose synthase. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970) which teaches "That paragraph (35 USC 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."

Applicant argues that the specification provides ample guidance to the skilled artisan for practicing the invention broadly. In particular, the specification discloses in detail how to clone DNAs encoding putative raffinose synthase enzymes. Applicant further argues that the specification provides details such as organisms likely to be useful for isolating template genomic DNA or cDNA (see, e.g. page 1, lines 9-14) and methods for cloning DNA encoding a putative raffinose synthase enzyme from an RNA fraction, including an extensive list of primers that can be utilized for PCR amplification from templates obtained from different organisms (see, e.g. page 10, line 11 to page 18, line 14). Applicant additionally argues that the specification describes methods for expressing the cloned DNA in plant cells and in bacteria (see, e.g. page 24, line 3 to page 27, line 23) and an example of expression in bacteria (Example 8 beginning at page 39). Additionally Applicant argues that the specification describes how to purify raffinose synthase from plant cells (see, e.g. Example 3 beginning on page 32). As a result, the specification describes a biochemical assay for raffinose synthase, referring to the Lehle article noted above and summarizing the procedure in Example 2 beginning at page 31. The specification also provides a number of working examples of isolation of partial or complete raffinose synthase genes from a number of different plants. See Examples 7 and 9 to 11 and of transformation of a plant (soybean) with a cloned DNA encoding a raffinose synthase (Example 13). See the section spanning pages 22-23 of the Appeal Brief.

Applicant argues that applicants have provided evidence to support an assertion that one of ordinary skill in the art can readily distinguish a RFS from a STS or a SIP.

The Nagasawa Declaration demonstrates unequivocally that the RFS subfamily of glycoside hydrolases (see Applicants' discussion of Peterbauer *et al*, below) is easily distinguished from the STS or SIP subfamilies of glycoside hydrolases on the basis that RFSs are more similar to each other, and STSs are more similar to each other, than RFSs are similar to STSs. Applicant argues that this relationship among their amino acid sequences can be used to construct a "molecular phylogenetic tree" upon a branch of which any particular amino acid sequence thought to represent a RFS or STS (or SIP) can be placed. Applicant further argues that the Nagasawa Declaration additionally explains that this analysis is robust in its conclusions (though perhaps the specific degrees of sequence similarity may vary) to three different approaches to sequence similarity analysis. See the paragraph spanning pages 23-24 of the Appeal Brief.

These arguments are not found to be persuasive. The instant application only provides guidance on how to make and use one species of raffinose synthase encoding nucleic acid, that being a nucleic acid encoding SEQ ID NO: 2, a broad bean raffinose synthase. The Examiner has established that those skilled in the instant art recognize that cloning DNA is routine, but determining what the cloned DNA encodes requires additional steps, and that one of skill in the art cannot presume encoded function simply based on sequence similarity. As pointed out previously, Osumi *et al* (U.S. Patent 6,891,084) teach a soybean raffinose synthase enzyme at SEQ ID NO: 24, [a sequence alignment attached hereto) shows only 32.9% sequence identity at the amino acid level with Applicant's SEQ ID NO: 4. Applicant's own arguments of record concerning structure-function relationship among raffinose synthase enzymes that distinguish them

from stachyose synthase enzymes would suggest that Applicant's SEQ ID NO: 4 does not teach a raffinose synthase. See the Nagasawa Declaration filed under 37 CFR § 1.132 on 12 September 2005, page 7. In Table 1 of The Nagasawa Declaration, six (6) proteins are listed as raffinose synthase, Sc-02 and Sc-04 being taught in the instant application, and Aj-05 being the cucumber raffinose synthase of the prior art acknowledged in the Information Disclosure Statement filed on 5 March 2001. Sc-03 and Sc-05 are taught in a related application assigned to the Applicant, which has a foreign priority of 30 April 1998, and PsRFS (pea raffinose synthase) was taught by Peterbauer *et al* in 2002. Given the U.S. filing date of 18 December 1997 of the instant application, only two complete and confirmed raffinose synthase enzyme amino acid sequences, one being the asserted raffinose synthase of SEQ ID NO: 4, were know in the art at the time of the instant invention. The Examiner has established the fact that at the time of the instant invention, only one other plant raffinose synthase "gene" was known in the art, that being from cucumber and disclosed in US Patent 6,166,292 (see Office action mailed 6 February 2002, page 5). It is unclear how Applicant at the time of filing could make an assumption of function of an encoded "enzyme" using sequence similarity without actually showing the expressed encoding nucleic acid actually produced a raffinose synthase at the time of the instant invention.

Applicant argues that claims 59-62 relate to chimeric genes comprising the isolated nucleic acids described in claims 6, 43 and 48-53, operatively linked to a promoter. Applicant asserts that the Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained

above, and therefore the various arguments applied to claims 46-53, as may be applicable, should be applied to these claims as well. See page 26, 4th paragraph of the Appeal Brief.

Applicant argues that claims 65 and 66 relate to plasmids comprising the isolated nucleic acids described in claims 6, 43 and 46-53. Applicant argues that claims 63, 64 and 67-72 relate to transformants and host organisms transformed with chimeric genes or plasmids described in claims 59-63 or 65-66 (see page 27, 2nd paragraph of the Appeal Brief). Applicant argues that claim 73 is directed to a method for metabolic modification of a plant using the cloned DNA described in claim 52 (see page 27, 3rd paragraph of the Appeal Brief). Applicant argues that claim 74 is directed to a method for metabolic modification of a plant using the cloned DNA described in claim 53 (see page 28, 1st paragraph of the Appeal Brief). Applicant asserts that the Examiner has not set forth any particular explanation of any separate reason for lack of enablement other than those explained above, and therefore the various arguments applied to claims 46-53, as may be applicable, should be applied to these claims as well. See page 27, 1st paragraph of the Appeal Brief.

Applicant argues that claim 78 is directed to isolated nucleic acids within claim 52 encoding either the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Thus, the breadth of claim 78 encompasses fewer embodiments compared to the scope of claim 52 and the predictability of the art is somewhat higher. Applicant further argues that the amount of

experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; e.g. the nucleic acid encoding this amino acid sequence can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. See page 28, 2nd paragraph of the Appeal Brief.

These arguments are not found to be persuasive. The Examiner has brought into question whether the specification teaches one of skill in the art how to use a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 4 using the guidance of the specification without knowing what function the amino acid sequence has.

Applicant argues that claims 79 and 80 are directed to the subset of the chimeric genes of claims 59 and 65 in which the portion encoding an amino acid sequence encodes either the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Applicant further argues that the breadth of claims 79 and 80 encompass fewer embodiments compared to the scope of claims 59 and 65, and the predictability of the art is somewhat higher, and that the amount of experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; e.g. the nucleic acid encoding this amino acid sequence can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8.

See the paragraph spanning pages 28-29 and page 29, 2nd paragraph of the Appeal Brief.

Applicant argues that claim 81 is directed to methods for metabolic modification of a host organism utilizing a subset of the nucleic acids within the scope of claim 73 in which the nucleotide sequence encodes either' the amino acid sequence of SEQ ID NO: 2, which is demonstrated to have RFS activity, or SEQ ID NO: 4, a full length protein sequence having 75% identity to SEQ ID NO: 2 and thus very likely to demonstrate RFS activity. Applicant argues that the breadth of claim 81 encompasses fewer embodiments compared to the scope of claim 73 and the predictability of the art is somewhat higher. Furthermore, the amount of experimentation needed to test operability of a protein of amino acid sequence of SEQ ID NO: 4 is very small and such experimentation is very well guided by the specification; e.g. the nucleic acid encoding this amino acid sequence can be encompasses fewer embodiments compared to the scope of claim 61. Applicant further argues that the specification examples 5-8 describe a species within the scope of claim 83, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 83, is cloned and demonstrated to encode a protein having RFS activity. Applicant also argues that a second embodiment within claim 83 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 83 and a nucleic acid from soybean, which is another leguminous plant, and that the experimentation required to demonstrate that nucleic acids within the scope of claim 83 encode an active RFS is

slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. See the paragraph spanning pages 29-30 of the Appeal Brief.

Applicant argues that claim 82 is directed to isolated nucleic acids within the scope of claim 53, in which the nucleic acid of the portion encoding an amino acid sequence is obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Applicant argues that the breadth of claim 82 encompasses fewer embodiments compared to the scope of claim 53. Applicant furtherr argues that the specification examples 5-8 closely describe a species within the scope of claim 82, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 82, is cloned and demonstrated to encode a protein having RFS activity, and that a second embodiment within claim 82 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS (SEQ ID NO: 4) is cloned using some of the primers recited in claim 82 and a nucleic acid from soybean, which is another leguminous plant. Applicant argues that the experimentation required to demonstrate nucleic acids within the scope of claim 82 encode an active RFS is slight, and such experimentation is very well guided by the specification, for example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. See page 30, 2nd paragraph of the Appeal Brief.

Applicant argues that claims 83 and 84 are directed to chimeric genes and plasmids, respectively, within the scope of claims 61 and 66, in which the nucleic acid of the portion encoding an amino acid sequence is obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. Thus, the breadth of claim 83 encompasses fewer embodiments compared to the scope of claim 61. Applicant further argues that the specification examples 5-8 describe a species within the scope of claim 83, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 83, is cloned and demonstrated to encode a protein having RFS activity. Applicant also argues that a second embodiment within claim 83 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 83 and a nucleic acid from soybean, which is another leguminous plant. The experimentation required to demonstrate that nucleic acids within the scope of claim 83 encode an active RFS is slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. See pages 30-31 of the Appeal Brief.

Applicant argues that claim 85 is directed to a method for metabolic modification within the scope of claim 74, in which nucleic acids are used that are obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of

these sequences, thus the breadth of claim 85 encompasses fewer embodiments compared to the scope of claim 74. Applicant further argues that the specification examples 5-8 describe a species within the scope of claim 85, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 85, is cloned and demonstrated to encode a protein having RFS activity, and that a second embodiment within claim 85 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 85 and a nucleic acid from soybean, which is another leguminous plant. Applicant argues that the experimentation required to demonstrate a nucleic acid within the scope of claim 85 encodes an active RFS is slight, and such experimentation is very well guided by the specification, for example the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. See page 32, 2^{hd} paragraph of the Appeal Brief.

Applicant argues that claim 86 is directed to isolated nucleic acids within the scope of claim 77, in which nucleic acids are used that are obtained by amplification of a nucleic acid obtained from a leguminous plant utilizing specified primers that hybridize to either SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of these sequences. thus the breadth of claim 86 encompasses fewer embodiments compared to the scope of claim 77. Applicant further argues that the specification examples 5-8 describe a species within the scope of claim 86, in that a cDNA encoding RFS from broad bean, a leguminous plant, utilizing some of the primers set forth in claim 86, is cloned and

demonstrated to encode a protein having RFS activity. Applicant argues that a second embodiment within claim 86 is described in the examples, in that a cDNA encoding a protein having a degree of sequence identity to SEQ ID NO: 2 sufficient to identify it as a RFS is cloned using some of the primers recited in claim 86 and a nucleic acid from soybean, which is another leguminous plant, and that the experimentation required to demonstrate a nucleic acid within the scope of claim 86 encodes an active RFS is slight, and such experimentation is very well guided by the specification. For example, the nucleic acid can be substituted for that encoding SEQ ID NO: 2 as described by the working example 8. See the paragraph spanning pages 32-33 of the Appeal Brief.

These arguments are not found to be persuasive. Because the claimed chimeric gene comprises the isolated nucleic acid of claims 52-58, claims 59-62 lack enablement for the same reasons. The application only teaches one isolated nucleic acid encoding a raffinose synthase enzyme, in addition to one functionally uncharacterized coding sequence and two partial coding sequences of unknown function. Only one species of the four recited in claim 78, for example, are enabled for the claimed invention. In the same manner, the plasmid of claims 65 and 66, the transformant and host organism of claims 63, 64 and 67-72, and the metabolic transformation aspect of claim 73 or 74 lack enablement because they comprise nucleic acids that have not been fully enabled. The Examiner has not argued that the promoter aspect lacks enablement, just the nucleotide sequence coding for an amino acid sequence of a raffinose synthase as broadly claimed lacks enablement.

Double Patenting

7. Claims 46, 47, 52, 53, 55 and 59-77 and 78-86 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 16-23 and 28-30 of copending Application No. 09/301,766. Applicants do not address this rejection in the Appeal Brief.

Conclusion

8. Claims 6 and 43 are allowed.

9. Claims 46-86 remain rejected.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached at (571) 272-0975. The central FAX number for official correspondence is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (571) 272-1600.

/David H Kruse/
Primary Examiner, Art Unit 1638
17 June 2008

/Anne Marie Grunberg/
Supervisory Patent Examiner, Art Unit 1638